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Tobacco, respiratory diseases, cardiovascular risk, and cancer: Classical approaches and new alternatives

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Abstract

Smoking tobacco is the main preventable aetiological factor of mortality worldwide, with a significant impact on respiratory and cardiovascular diseases and cancer. Smoking cessation and prevention must be prioritized in health care and legislative initiatives to reduce mortality and associated complications. To date, pharmacological treatments and behavioural therapies, along with community strategies, have been shown to be the most effective methods, especially when used in combination with a coordinated approach. However, their efficacy remains suboptimal and diminishes over time due to the high frequency of relapse. Data from the survey on alcohol and other drugs in Spain (*EDADES*) of the Spanish National Health System showed that the percentage of smokers has hardly decreased in recent decades and that many smokers do not intend to give up smoking, even those who have already suffered from some complications. In this context, the development of new products such as electronic cigarettes and heated tobacco may have some application in the population. The *FDA* recognition of risk-modifying products, the British Health System reports on electronic cigarettes, and the recommendations of the *American College of Cardiology* expert consensus on smoking cessation, among others, indicates the need to consider updating the multifactorial and multidisciplinary approach of smoking and its consequences.

Keywords: Tobacco; Pharmacological treatment; Behavioural therapy; Tobacco risk-modifying products

1. Introduction

Smoking tobacco is the leading preventable cause of mortality worldwide, significantly impacting respiratory and cardiovascular diseases, as well as cancer (1-2). According to WHO data, although the number of smokers has decreased in recent decades, its prevalence is still high (3). Data from the *EDADES* study of the Spanish Ministry of Health estimated a smoking prevalence of 33.1% in 2022, which is slightly lower than the rate of 34.1% reported in 1997 (4). Notably, according to data from the above survey, 35.8% of smokers do not contemplate giving up smoking, and 22.3% of those who have decided to quit have never actually tried to do so (4). This scenario, therefore, requires a broad and multifactorial approach, including not only all health and legislative strategies aimed at smoking cessation and harm reduction but also those alternatives for cases in which the above are not feasible or effective.

Given its clinical consequences, the continuation of smoking in those subjects who have already developed some complications is particularly noteworthy. Smoking is the cause of 85% of cases of chronic obstructive pulmonary disease (COPD), which can develop in one out of every 4 smokers (5-6). However, between 29% and 48% of COPD patients still smoke despite having developed the disease (7,8). In fact, 24% of patients who state that they have quit

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smoking show carbon monoxide values on co-oximetry that are compatible with smoking (9). A wide range of interventions exist to help COPD patients quit smoking or to at least reduce its impact.

Cardiovascular diseases are the main cause, over respiratory diseases and cancer, of mortality in smokers. Smoking increases the incidence of acute myocardial infarction by 3 to 6 times in men and women, respectively, and is responsible for 65–92% of premature coronary heart disease cases and 24–56% of cases in those over 45 years of age (10). Even considering the evidence that smoking cessation reduces cardiovascular mortality after a heart attack by 71% (11), data from the *EUROASPIRE-V* study indicate that up to 34% of patients with established cardiovascular disease continue smoking (12). The results of a meta-analysis revealed that smoking cessation reduces the risk of cardiovascular death by half compared continuing to smoke (13). Therefore, there is no doubt that targeting the harmful effects of smoking is the most effective measure, even above pharmacological treatment, to reduce cardiovascular morbidity and mortality in patients who smoke.

Moreover, smoking has been associated with multiple types of cancer, and its impact on reduced survival after diagnosis is widely documented (14,15). A longitudinal study in Australia revealed that after the diagnosis of a primary cancer, 63% of patients who were smokers remained active 6 months after diagnosis, and only 10% of those who intended to quit smoking had actually quit smoking by 2 years (16). In a meta-analysis that included 36 studies and a behavioural and pharmacological intervention, between 5.2% and 75% of patients diagnosed with cancer enrolled in randomized clinical trials quit smoking permanently, whereas this percentage decreased to 15–46% in patients enrolled in longitudinal studies under real-life conditions (17). An interesting recent meta-analysis suggested that multiple approaches with cognitive-behavioural and pharmacological measures or even behavioural measures alone are more effective than pharmacological treatments alone in preventing cancer patients from smoking (OR 1.67; 95% CI 1.24–2.26 vs. OR 1.11; 95% CI 0.69–1.78 for combined treatment vs. isolated pharmacological treatment) (18). Thus, there is a broad opportunity to improve strategies aimed at getting cancer patients to quit smoking tobacco, as well as to reduce its toxic effects that progress the disease and interfere with treatments.

2. Multifactorial approach to smoking cessation

Encouraging permanent smoking cessation is the main sociohealth objective to decrease and reduce the risks to the smoking population with or without associated diseases, as well as those of passive smokers. Furthermore, there is strong evidence that smoking cessation decreases cardiovascular complications, improves and at least partially reverses respiratory diseases, and improves survival and quality of life by reducing the adverse effects of treatment in cancer patients (19,20). However, definitive cessation is not always possible, with very frequent relapses; moreover, smokers themselves sometimes do not even intend to quit smoking, so the toxic effects of tobacco persist over time. Therefore, the possibility of exploring and implementing other alternatives to smoking cessation should be considered when previous cessation strategies have not been successful. Accordingly, smoking cessation strategies should include, in order of priority:

2.1. Strategies aimed at permanent cessation of tobacco use

- Pharmacological
- Nonpharmacological
- Tobacco risk-modifying products

2.1.1. Pharmacological strategies

Pharmacological treatment is a cornerstone of smoking cessation, although it is often unsuccessful or leads to relapses. It often achieves better results when combined with other nonpharmacological strategies, as well as when funding is available, as will be addressed later.

The drugs included in the first-line treatment are nicotine in its various formulations, bupropion, varenicline and cytisine (Table 1). Additionally, antidepressants and anxiolytics, among others, may be used as second-line drugs. In this review, the different studies were evaluated according to the level of evidence: A (high), B (moderate) or C (low).

Considering the relevance of financing in the outcome of smoking cessation, it is essential to identify the particular circumstances in each region. Currently, cytisine, varenicline, and bupropion are financed in Spain. However, the different formulations of nicotine are not financed. Despite these limitations, it is necessary to consider all drugs when approaching smoking cessation, given the diversity of the evidence, both in clinical trials and in longitudinal studies under real-life conditions.

Table 1 First- and second-line drugs used for smoking cessation with their level of evidence (LE) (Adapted from sources 25, 28, 30, 32, 52)

Drug	Formulation	Dosage (mg)	Mechanism of Action	Adverse Effects	Efficacy vs. Placebo OR (95% CI)	Efficacy Combinations	Comments
Nicotine	Patches	21/14/7 (if ≥10 cig/day) 6-2-2 weeks 14/7 (if <10 cig/day) 6-2 weeks	Stimulation of acetylcholine nicotinic receptors and possible mid-term reduction in receptor numbers.	Skin reactions, nightmares, nausea, oral irritation, gastrointestinal discomfort.	2.02 (1.52-1.77) (global for all formulations) LE = A	1.25 (1.15-1.36) NCT monotherapy vs. NCT combination LE = B	Caution in patients with recent MI, arrhythmias, angina and pregnant women and adolescents (all formulations).
	Gum	14/7 (if <10 cig/day) 6-2 weeks 4 2 (8-12/day for 3 months)		Nausea, oral irritation, gastrointestinal discomfort, hiccups, TMJ disorders.			Can be combined with patches. Dose control needed.
	Tablets	4 2 (1 every 1-2 hours up to a maximum of 20 for 3-6 months)		Nausea, vomiting, sleep disturbance, mydriasis.			Dose control needed.
	Nasal Spray	0.5-1/1-2 h for 3-6 months					
Bupropion	Tablets	150 for 4 days 150/12 h for 3-6 months	Not well known, likely inhibition of dopamine and norepinephrine reuptake.	Insomnia, agitation, dry mouth, headache.	1.43 (1.26-1.62) [71 RCT n=14759] LE = A	BP+VRC or BP+NCT vs. placebo nd 1.35 (1.12-1.64) BP+NCT vs. BP LE = B	Do not use in cases of epilepsy or alcohol abuse. Caution in pregnant women, adolescents and patients with liver impairments.
Varenicline	Tablets	0.5/24 h for 3 days 0.5/12 h for 3 days	Selective partial agonist of α4β2 nicotinic/acetylcholine receptors.	Nausea, insomnia, headache, possible adverse reactions in psychiatric patients.	2.33 (2.02-2.68) [67 RCT n=16430] LE = A	6.08 (3.47-10.66) VRC+BP vs. VRC+NCT 5.75 (2.77-	Take with water and food. Caution in adolescents and pregnant women.

		1/12 h for 3-6 months				14.88) VRC+NCT vs. placebo LE = B	
Cytisine	Tablets (1.5 mg)	Progressive reduction from 6 to 1 tab. in 25 days	Selective partial agonist of α4β2 nicotinic/acetylcholine receptors.	Nausea, vomiting, insomnia, nightmares.	2.21 (1.66-2.97) [7 RCT n=3848] LE = A	Cytisine vs. VRC: nd Cytisine vs. NCT: nd Low evidence	Cease smoking during treatment to avoid nicotine poisoning.
Nortriptyline	Tablets	150 for 7 days 300 for 2 more weeks	Inhibits noradrenaline and serotonin reuptake in the CNS.	Dry mouth, sedation, constipation, urinary retention, blurred vision, glaucoma.	1.35 (1.02-1.81) [10 RCT n=1290] LE = B	2.33 (1.21-1.47) NTP+NCT vs. placebo LE = B	
Selegiline	Tablets (1 mg)	1 every 12 hours	CNS MAO-B inhibitor responsible for dopamine degradation.	Dizziness, nausea, stomach pain, constipation, mouth ulcers, insomnia.	1.16 (0.63-2.12) LE = B	5.67 (1.15-28.00) SEL+NCT vs. placebo LE = B	
Fluoxetine	Tablets (20 mg)	20 initially 40 for 2-3 weeks	Selective serotonin reuptake inhibitor.	Nausea, insomnia, reduced libido, sexual disorders, tremors.	0.67 (0.20-2.18) LE = B	0.72 (0.30-1.74) FLX+NCT vs. NTP LE = C	Low evidence.

Abbreviations: MI: myocardial infarction; TMJ: temporomandibular joint dysfunction; BP: bupropion; RCT: randomized controlled trial; FLX: fluoxetine; CI: confidence interval; NCT: nicotine; NTP: nortriptyline; nd: no difference; OR: odds ratio; SEL: selegiline; VRC: varenicline. LE: Level of evidence. A = high evidence; B = moderate evidence; C = low evidence

2.1.2. Efficacy of first-line drugs

First, it is important to consider that most of the studies are of moderate or low quality and that comparisons between drugs are often indirect; thus, the level of evidence in most cases is not very high (evidence levels B and C, respectively).

Overall, all the drugs are superior to the placebo, as shown in Table 1 (level of evidence A). From a comparative point of view, varenicline has generally been shown to be superior in smoking cessation efficacy to nicotine monotherapy, bupropion and cytisine (21). Notably, in most studies, the assessment of smoking cessation is analysed in the short and medium term and rarely exceeds 12 months. In a study comparing varenicline and nicotine patches, the rates of smoking cessation at the end of treatment were 55.9% and 43.2%, respectively ($p<0.001$) (22). However, cessation after 52 weeks was reduced in both arms to 26.1% and 20.3%, respectively (22), which highlights the low efficacy of long-term pharmacological monotherapy.

In general, varenicline has several advantages over other first-line drugs:

- In terms of its posology, it is easy to administer, its adverse effects are rare, and it has hardly any pharmacological interactions.
- Unlike other drugs, smoking should not be stopped at the beginning of treatment. A smoking cessation date should be established, which may be after the start of treatment, usually between 8 and 35 days after the start of treatment.
- Prolonging treatment for up to 6 months increases the percentage of smoking cessation, unlike nicotine and cytisine, for which the likelihood of successfully quitting smoking is dose-dependent and not time-dependent (23).
- Regarding the use of different drugs in cases of previous failure, varenicline has been shown to have a favourable effect when treatment is repeated, whereas for bupropion and nicotine, the effect is null or of very low magnitude (24).
- Combinations of first-line drugs have been shown to be superior in efficacy to the different monotherapies (level of evidence B). When the combinations are analysed, those that include varenicline show a superior effect. In particular, varenicline and bupropion have been shown to be the best combination (25), whereas the combination of varenicline with nicotine at different combinations and doses has been shown to be superior to the individual drugs. The combination of bupropion with nicotine has not been shown to improve the cessation rate (26).

Compared with other drugs, cytisine is currently publicly funded in Spain. In general, cytisine has been shown to be similar or slightly superior to nicotine regarding smoking cessation (level of evidence C) but has a higher incidence of adverse effects, such as nausea, vomiting and sleep disturbances (27). Compared with varenicline, cytisine has similar efficacy, although it may have a more favourable cost-effectiveness profile (28). There is little evidence comparing cytisine with bupropion, and the evidence for their combination is scarce and of low quality.

2.1.3. Use of first-line drugs in particular situations

Cardiovascular disease is the main complication of tobacco toxicity, so there is often a need to address smoking cessation in patients who have experienced cardiovascular events. In addition to the previously mentioned probabilities of success, the severity and characteristics of the cardiovascular event are used to help determine the best smoking cessation strategy. Regarding intervention during the acute phase of the cardiovascular event, if pharmacological intervention is necessary, it may be advisable to act after the acute phase, although the level of evidence is low (C). When pharmacological intervention is necessary, it should be intensive. Some meta-analyses suggest that the combination of varenicline and nicotine is the pharmacological therapy of choice in patients with cardiovascular disease and is superior to the combination of bupropion and nicotine (level of evidence B) (29). However, evidence on cytisine is scarce. Regardless, both varenicline and nicotine in their various formulations and bupropion have been shown to be safe and not to increase long-term cardiovascular event rates (29).

With respect to COPD, the strategy should be intensive and, in most cases, should include a combination of drugs, specifically, varenicline and nicotine, preferably in the form of patches (30) (level of evidence B). Alternatively, varenicline can be used in a prolonged form or nicotine at high doses or combined with different formulations. The evidence concerning bupropion is controversial. Some studies suggest that it may worsen the ventilatory response to hypoxia and hypercapnia, impairing the evolution of the disease, although other specific studies have not demonstrated this effect (31). Compared with those of varenicline, the results are also heterogeneous in terms of efficacy in smoking cessation, so it is considered a second-line drug to be used in very specific situations.

For mental illnesses such as depression and other psychiatric pathologies, first-line drugs are usually the drugs of choice, with the combination of varenicline and bupropion being the most effective (level of evidence B) (32). Patients with depression tend to smoke more frequently and have greater difficulty quitting smoking. Moreover, smoking is associated with worsening mental health in these patients, whereas cessation has the opposite effect. It should be considered that nicotine has an antidepressant effect such that its deprivation increases depressive symptoms. In this field, in addition to first-line drugs, other antidepressants, including fluoxetine, nortriptyline and selegiline, can be used as complementary or adjuvant treatments. In a recent meta-analysis, nortriptyline or selegiline in combination with nicotine was shown to have a beneficial effect on smoking cessation compared with a placebo (OR 2.33 and 3.78, respectively) (33). Therefore, this combination may be a second option when there are contraindications or poor responses to first-line drugs (level of evidence C). Findings from the same study suggest the use of the combination of varenicline and bupropion in patients with significant mental illness.

2.1.4. Nonpharmacological strategies

The nonpharmacological strategies and therapies used for smoking cessation are multiple and diverse (Table 2). The results in terms of efficacy in smoking cessation are heterogeneous, even within the same intervention. Differences in the population and in the type of intervention, difficulty in measuring the objectives in a standardized approach, and variability of individuals involved in applying the different strategies may explain, at least partially, the differences between them. In general, most of the studies have evidence of a level C.

Table 2 Nonpharmacological interventions in smoking cessation

Type of intervention	**Comments**
Basic Intervention Professional advice (doctor, nurse) Motivational interviewing Information leaflets, self-help material Manuals Videos	Should be implemented in most situations Cost-efficient Should be quick and brief Efficacy between 5-10% in smoking cessation Advisable to accompany with complementary materials When intensive, its efficacy increases
Psychological Treatments Cognitive behavioural therapy Aversive therapies Multicomponent programmes	More effective in motivated patients and when other treatments have failed Cognitive-behavioural therapy is preferable to aversive therapy with a cessation rate of 20-25% Whenever possible, combine strategies and techniques
Technology-based Strategies Telephone Internet: e-health Laptop applications (App): m-health Artificial intelligence	Accessibility Feedback Longitudinal follow-up Reinforcement techniques Great potential for development Interactivity
Legislative and Community Programs	
Other Techniques with Low/Weak Evidence Hypnosis Acupuncture Sensory deprivation Physical exercise	Although they have been used, there is no conclusive evidence on their benefits and success rates

Many different interventions can be conducted in group or individual forms, often depending on individual preferences and the health care system's capabilities.

A recent meta-analysis of the different nonpharmacological options in smoking cessation programs revealed that professional counselling, cognitive behavioural therapy and nicotine-free electronic cigarettes are the most widely used options (34), although their efficacy depends on the characteristics of the different programs implemented. Strategies based on new technologies are also becoming increasingly popular. Although electronic cigarettes without nicotine have not been approved as a treatment for smoking cessation, multiple studies have been performed and will be analysed later in this review.

Cognitive-behavioural therapy is aimed at modifying smokers' behaviour so that their knowledge, attitudes and actions help them cope positively with smoking habits and can be implemented both in groups and individually. The different techniques available include professional advice, self-help materials, motivational interviewing, internet messages and telephone counselling, with results varying according to the time and methodology of evaluation. Data from a meta-analysis revealed a high level of evidence that professional counselling has greater efficacy than other techniques, such as text messages, which at least partially supports its good cost-effectiveness (OR 1.443; 95% CI 1.22-1.70) (35). This beneficial effect is enhanced when cognitive treatment complements pharmacological treatment regardless of the drug and the intensity of therapy (36). The efficacy of the different techniques used in behavioural psychotherapy also varies according to the objective, with videos and self-help materials being more effective in the short term (7 days), individual interviews being more effective in the medium term (30 days), and motivational interviews and economic incentives, including pharmacological funding, being more effective in the long term (definitive abstinence) (37).

The impact of new technologies on smoking cessation, although promising, has not been clearly defined. Moreover, most studies evaluate short periods of time, up to a maximum of one year. In a meta-analysis evaluating the effects of different technologies applied to smoking cessation, the use of text messaging (SMS) reduced smoking cessation compared with basic support by 50% and 23% at 3 and 6 months, respectively (RR 0.50; 95% CI 0.25–0.75 and RR 0.77; 95% CI 0.49–1.04) (level of evidence B) (38), without the frequency of SMS influencing the effect. The benefits were confirmed independently of whether the measure of smoking cessation was biochemical or self-reported. Another meta-analysis confirmed that intervention with new technologies increased the cessation rate (RR 1.86; 95% CI 1.69-2.04) as well as long-term abstinence (RR 1.79; 95% CI 1.60-2.00) (39). This effect was confirmed for the use of phone calls, SMS, apps or web pages.

A further step in the development of new technologies is the impact of artificial intelligence (AI). Although there is still little evidence, a meta-analysis of five studies revealed that more patients in the intervention group (AI) quit smoking at 6 months than did those in the control group (RR 1.29; 95% CI 1.13-1.46) (40). An important consideration in the use of AI is to avoid disconnection between clinicians and patients, as in this case, losses increase, and the efficacy of the intervention therefore decreases. Maintaining the clinician–patient relationship when new technologies are used is critical to the success of programs, especially in the long term (41). A current limitation is the definition of AI, which is very broad and variable and can make interpretation of the results difficult.

The effects of exercise on smoking cessation are very contradictory. In most cases, the benefit is limited to the period during which the exercise program is carried out, and the effect ends with the completion of the program (42). A recent Cochrane review concluded that exercise has no clear beneficial effect on smoking cessation compared with basic support (43). However, exercise undoubtedly has very relevant additional benefits for patients who smoke, and for this reason, it should be included in the overall smoking cessation strategy.

2.2. Tobacco risk-modifying products

Recently, a variety of products have been developed with the aim of replacing conventional tobacco (CT) with, at least theoretically, products that are less toxic to human health. The products most developed as tobacco risk modifiers (TRMPs) are electronic cigarettes (ECs) with or without nicotine and heated tobacco products (HTPs).

From a conceptual point of view, these are compounds that, although not confirmed to be innocuous, reduce toxicity and, consequently, could reduce the harm and risk to health compared with CT. The concept itself generates controversy and differing views of their usefulness, since, as they are relatively recent products, there are no studies that evaluate their long-term health effects. However, studies performed in the short and medium term, including independent studies, have demonstrated a lower level of toxicity when using these products as opposed to CT and a possible benefit as shown by biomarkers and intermediate biological parameters compared with those of patients using CT (44).

PMRTs are not intended to replace classical pharmacological and nonpharmacological treatments with different smoking cessation strategies. Tobacco cessation is the best option to combat its toxic effects; however, in situations in which the results are not satisfactory, other alternatives, such as PMRTs, can be considered preferable options to continue smoking or reduce the amount of CT. This broad view of approaching smoking is at least partially supported, as the FDA has recognized PTCs as an alternative to reduce exposure to the toxic components of CT (45), a recent *Cochrane* review considers CE as an alternative to smoking cessation (46), the *Public Health of England* endorses the use of CE as a smoking cessation tool (47), and *the American College of Cardiology* considers the use of PTCs to reduce the cardiovascular damage of CT (48).

2.2.1. Electronic cigarettes

ECs or vapers are electronic devices containing liquid components that, when heated, deliver nicotine in aerosols of approximately 1.6–19 mg/cartridge (49). The liquid components include different flavours, sweeteners, glycerine, propylene glycol and others, which may attract smokers and sometimes nonsmokers, with the latter being a factor to be considered. The nicotine supply replaces the nicotine in the TC, thus contributing to a decrease in or cessation of TC consumption, although smokers' satisfaction is usually lower with the EC. Notably, nicotine, as a substance, is highly addictive and has effects on all body systems, such as increased sympathetic tone, vasoconstriction, elevated blood pressure and increased heart rate. However, it does not appear to increase the risk of cancer or to be associated with an increase in cardiovascular events (50), as the CNS is the source of its addictive effect and, subsequently, the toxicity of TC.

As previously mentioned, and as recommended in some countries, CE may be useful for reducing the consumption of TC or even achieving abstinence in smokers. Different studies and public institutions, such as the *Public Health of England,* have reported higher cessation rates than studies on traditional monotherapy strategies (level of evidence B) (51,52). Compared with nicotine replacement therapies, ECs increase cessation rates (RR 1.69; 95% CI 1.25–2.27) (31). Another study comparing the effects of EC with different doses of nicotine and without nicotine showed that at 12 months, 23% of smokers with EC with nicotine had reduced TC consumption by at least 50% compared to 4% of smokers with EC without nicotine (53). Therefore, EC may be useful for definitive or partial smoking cessation in some smokers.

The effect of ECs on the cardiovascular and respiratory systems, two of the target systems of the tobacco, is a relevant issue. The potential benefits arise from reduced consumption of CT and, therefore, from reduced exposure to its toxic substances. One study revealed that switching from BT to CE reduced exacerbations in COPD patients by 40% after five years (2.3 vs. 1.1%, smokers vs. CE, respectively), an effect that was maintained even in dual smokers (BT + CE) (level of evidence C) (54). Other studies have shown improvements in different parameters of lung function, including FEV1 (55). In the cardiovascular field, several studies have shown improvements in the markers of atherosclerotic disease in vapers compared with those in CT smokers (56,57). In terms of morbidity, in contrast to BT, in which the association with myocardial infarction (MI) is clearly demonstrated, there is no consistent scientific evidence showing a clear relationship between MI and CE (58).

As suggested by the various public and private institutions mentioned above, SC may be an effective alternative to reduce or cease the consumption of TC in those patients who are smokers who continuously do not benefit from conventional pharmacological and nonpharmacological strategies and in those who do not wish to quit smoking, in whom a reduction in health damage could be achieved at least theoretically, mainly regarding cardiovascular and respiratory diseases and cancer (level of evidence C) (59). It is also highly important to consider that ECs have not been shown to be completely harmless and that there are no long-term studies (decades) to ensure their safety. Another aspect to consider is that their formulation could be attractive due to flavour and sweeteners, which may involve a risk for adolescents and even induce consumption in nonsmokers, as has been suggested in some studies (60). The latter aspect should be adequately regulated and legislated, without this being an obstacle in using CE to reduce or even achieve abstinence from TC in those smokers in whom conventional strategies have repeatedly failed or in those smokers who do not wish to quit smoking.

2.2.2. Heated tobacco products

When tobacco is burned, more than 6,000 chemical components are generated, of which more than 150 are toxic to health and are responsible for smoking-related diseases. HTPs are formed by electronic devices that heat tobacco to approximately 350 °C but do not combust, thus decreasing the generation of the toxic and carcinogenic products of CT by 90–95% (61). In a study that analysed different toxic biomarkers of tobacco, it was concluded that patients who switched to HTPs reached levels similar to those who definitively ceased tobacco use (62). Moreover, HTPs contain tobacco, so they are more acceptable to smokers than ECs. Consequently, as they generate fewer toxic substances than TC, they may decrease the health risk, which explains why the FDA has considered them as tobacco risk-modifying products, unlike ECs (45).

Due to their lower toxicity and greater acceptance than ECs, HTPs may be used to aid smoking cessation, specifically either total cessation or a decrease in the consumption of TC, although few studies have evaluated this (level of evidence C). In a 3-year study of COPD patients, 60% of smokers who switched to HTPs achieved total abstinence, as assessed both subjective and by biochemical methods at the end of follow-up (63). Data from the same study revealed that dual smokers reduced their consumption of TC by 70%. Another study comparing cessation efficacy between HTPs and CEs revealed nonsignificant differences of 39.1% and 30.8% for HTP at 12 weeks (64).

The impact of HTPs on the respiratory tract is not fully understood. Longitudinal studies of sufficient duration have not been performed to determine with absolute accuracy the effects of CTP. Compared with CT, some studies have shown improvements in spirometry parameters, biochemical markers and symptomatic parameters in COPD patients who switched from CT to HTPs (65). Follow-up studies in COPD patients have shown a reduction in the number of exacerbations in patients who switched from CT to HTPs, which has been verified both in clinical trials and in real-life conditions (63,66). In a 24-month follow-up study, patients assigned to the PTC group showed less deterioration in lung function than those who continued to use CT (67). These data may be consistent with the lower toxicity of PTCs than of TCs. In contrast to these results, PTCs have not been shown to be harmless to the respiratory system. A large systematic review concluded that PTCs result in fewer respiratory complications than BT does but may be associated with a higher incidence of complications than that found in nonsmokers because of their possible impact on lung physiology and bronchial tract epithelial cells (68).

Considering the impact of CT on atherosclerotic disease, PTCs have also been studied in this field. In a large review of controlled clinical trials, it was concluded that CTP, compared with CT, reduces biomarkers of cardiovascular disease and improves cardiac functional parameters (69). Data from another systematic review corroborate how switching from CT to CTP improves most atherosclerosis-related parameters, including the lipid profile, platelet aggregation, oxidative stress, C-reactive protein, and leukocytes (70). Other studies, however, are not as conclusive (69). Thus, it is important to keep in mind that the possible benefit occurs when switching from TC to PTCs, which does not mean that exposure to PTCs improves cardiovascular risk.

To date, there is strong evidence that PTCs generate 90–95% fewer carcinogenic and health-damaging components than CT, although the long-term clinical significance of this lower toxicity has not yet been determined. There is also some evidence that switching from CT to PTC may modify and/or reduce the risk of COPD progression and the development of cardiovascular disease and cancer. However, to date, there are no longitudinal studies extensive enough to determine the safety of these products. Therefore, and considering the current evidence and the positioning of different public and private institutions, PTCs may be considered alternatives to reduce the risk of complications in compulsive smokers, those who refuse to quit smoking, and those in whom classical pharmacological and nonpharmacological strategies have repeatedly failed (Figure 1).

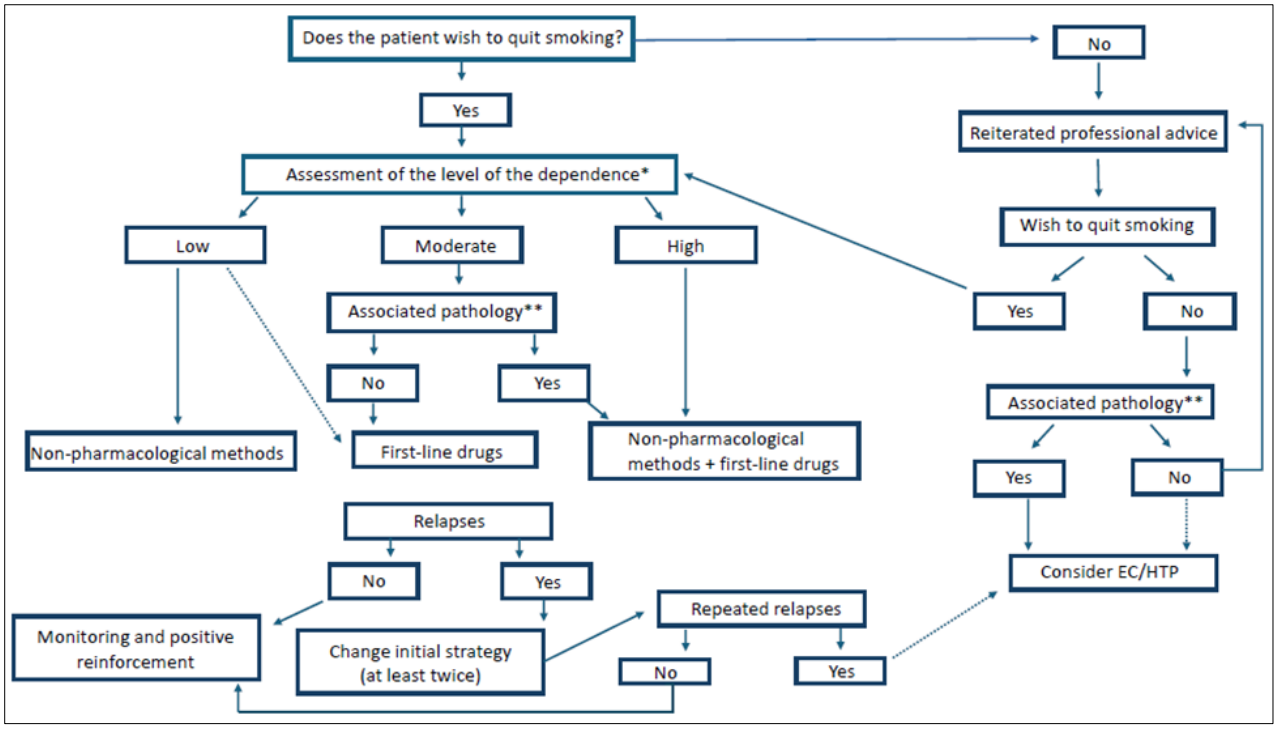

Figure 1 Proposed algorithm for smoking cessation. *Fagerström test (0-2: low dependence; 3-5: moderate; ≥ 6: high). **Chronic obstructive pulmonary disease, cardiovascular disease, cancer, mental illness. EC: electronic cigarettes. HTP: heated tobacco products. Solid line: preferred option. Dotted line: alternative option to be assessed according to patient characteristics

3. Conclusion

Smoking is the most significant modifiable risk factor for morbidity and mortality. The primary strategy to reduce the effects of smoking is permanent cessation. The combination of pharmacological treatment and cognitive–behavioural therapy, along with legislative measures, has been shown to be the most effective strategy.

Regardless of pharmacological availability, the combination of varenicline with bupropion and/or nicotine has been shown to be the most effective treatment, especially in smokers with a high level of addiction. Cytisine, which is currently publicly funded in Spain, shows similar efficacy in abstinence to varenicline, although there is insufficient evidence on its effects when it is combined with other drugs. Relapses are very common among smokers, so the implementation of different strategies should be considered.

Risk-modifying products should never be considered a first-line alternative, but they should be considered an option for compulsive smokers, those who refuse to quit smoking, and those who have repeatedly failed classical strategies.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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